REMARKS

The Office Action, the Advisory Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93, 95 and 98-120 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

In the Advisory Action, the examiner maintains the rejection of claims 93, 95 and 98-102 under 35 U.S.C. 103(a) as being unpatentable over Nakamura et al. (*Infect. Immun.* 61:64-70, 1993), stating as follows:

i) In the absence of evidence to the contrary, neither different physical forms nor purity of the same molecule would make the molecule itself different from each other, and it is less relevant when either form of the molecule or less purified molecule is used for generating antibodies because same antibodies would be generated so long as the same antigen is used.

ii) While the applicant argues that Nakamura's factor did not possess its activity when purified from SDS-PAGE, losing activity after SDS-PAGE does not indicate that Nakamura's factor differs from that of the present invention as there can be multiple reasons such as the use of reducing agent.

iii) While the applicant argues that Nakamura was not sufficient to allow one of ordinary skill in the art to obtain monoclonal antibodies, one or two publications focusing on a different issue (the factor) and not disclosing the antibody to the factor is not an indication that one of ordinary skill in the art was unable to obtain monoclonal antibodies based on Nakamura's teaching of the polypeptide factor.

With due respect to the examiner, applicants believe that the above statements i) to iii) by the examiner are not reasonable for the following reasons:

With regard to statement i)

IGIF of the present invention is a substance which has a molecular weight of 19,000 ± 5,000 daltons and is detected as a single band on SDS-PAGE.

On the contrary, it is considered that Nakamura's factor, even if it comprises the IGIF disclosed in Okamura et al. (*Infect. Immun.* 63:3966-3972 1995), is a mixture or a complex which includes a substantial amount of proteins other than IGIF (the molecular weight of Nakamura's factor is 50,000 to 55,000 daltons on SDS-PAGE and 70,000 to 75,000 daltons on gel filtration). It is believed that it would not have been obvious for one of ordinary skill in the art to obtain monoclonal antibodies to the IGIF alone using such factor.

In fact, according to Table 1 at page 66, right column of Nakamura et al., Nakamura's factor has a specific activity of about $2.8x10^5$ units/mg protein. By contrast, a specific activity of the IGIF of the present invention is about $5x10^5$ units/mg protein (please see page 41, line 21 of the specification). The specific activity of the Nakamura's factor is only 56% of that of the IGIF of the present invention even if the activity of Nakamura's factor is brought by the IGIF comprised in the factor. This indicates that Nakamura's factor comprises 44% (100%-56%) of unpurified proteins other than the IGIF. When one of ordinary skill in the art uses such unpurified protein as Nakamura's factor as an antigen to generate antibodies, it is clear that numerous kinds of antibodies would be generated and it would require undue experimentation to identify and isolate an antibody against only IGIF.

The antibody against the IGIF of the present invention is not an antibody obtained by using Nakamura's factor, but an antibody obtainable by using the IGIF having a specific activity of about 5×10^5 units/mg protein. However, even though Nakamura's factor comprises the IGIF, it would have been difficult to expect with a reasonable expectation of success that the antibody of the present invention is obtained by using Nakamura's factor without undue experimentation.

As mentioned above, the difference in purity between the IGIF of the present invention and Nakamura's factor is an important matter that influences the possibility of success in obtaining antibodies against the IGIF of the present invention. Thus, applicants submit that the examiner's statement in the Advisory Action that "neither different physical forms nor purity of the same molecule would make the molecule itself different each from each other, and it is less relevant when either form of the molecule or less purified molecule is used for generating antibodies because same antibodies would be generated so long as the same antigen is used" is unreasonable.

With regard to statement ii)

The examiner considers that Nakamura's factor losing activity after SDS-PAGE can be due to multiple reasons such as the use of reducing agent. However, it should be noted that the IGIF of the present invention does not lose its activity by the use of reducing agent. This property of IGIF serves to distinguish IGIF from IL-12, which is capable of inducing IFN-γ and is an IGIF-like substance. Okamura et al. also states at page 3969, left column, second paragraph, that IGIF does not lose its activity by the use of reducing agent.

The fact that Nakamura's factor loses its activity by the use of reducing agent indicates that Nakamura's factor is a

different substance from IGIF. Applicants therefore believe that it would have been difficult to obtain an antibody against IGIF using Nakamura's factor at the time the present invention was made, even if Nakamura's factor comprises IGIF.

In view of above, applicants submit that it is unreasonable for the examiner to state that the fact that Nakamura's factor loses activity after SDS-PAGE does not indicate that Nakamura's factor differs from that of the present invention as there can be multiple reasons such as the use of reducing agent.

With regard to statement iii)

The examiner's position relies on the premise that Nakamura's factor is same as IGIF. However, as mentioned above, this premise is not correct.

In general, an antigen is necessary to obtain an antibody. Whether a desired antibody is obtainable depends on the purity of an antigen as shown in the following statement in Sevier et al., *Clin. Chem.* 27(11) 1797-1806 (1981) a copy of which is attached hereto:

> Therefore, when one is producing monoclonal antibodies the purity of the immunogen need only be a concern if the antigenic site of interest is poorly immunogenic. To minimize screening problems when dealing with soluble antigens, the immunogen should be as pure as possible, because the purity of the immunogen may reflect the frequency of positive clones.

> (from page 1797, right column, the last line to page 1798, left column, line 6).

On the other hand, Lochner et al., Journal of Immunological Methods, 259:149-157 (2002), a copy of which is also attached hereto, states:

> IL-18-deficient mice were immunized (i.p.) twice (with a 4-week interval) using 25 or 50 μg rIL-18 (Peprotech EC, London, UK)… (page 150, right column, lines 20-22).

It should be noted that "rIL-18" is a recombinant IL-18 having high purity. Therefore, it is apparent that IGIF with high purity is required as an antigen in order to obtain an antibody against IGIF.

Applicants emphasize that it should be noted that Nakamura never obtained antibodies against IGIF. No prior art is cited and applied that discloses antibodies against IGIF. Accordingly, Nakamura does not and cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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